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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|-----------------|-------------|----------------------|---------------------|------------------|
| 10/057,620      | 10/25/2001  | Abraham Scaria       | 5046US              | 2242             |

7590            06/28/2005

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EXAMINER

WEHBE, ANNE MARIE SABRINA

ART UNIT

PAPER NUMBER

1633

DATE MAILED: 06/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/057,620             | SCARIA ET AL.       |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | Anne Marie S. Wehbe    | 1632                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 31 March 2005.
- 2a) This action is FINAL.                    2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) Claim(s) \_\_\_\_\_ is/are allowed.
- 6) Claim(s) 1-4, 17-22, 35-37 and 50-52 is/are rejected.
- 7) Claim(s) 5-16, 23-34 and 38-49 is/are objected to.
- 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  - a) All    b) Some \* c) None of:
    1. Certified copies of the priority documents have been received.
    2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
    3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_.
- 5) Notice of Informal Patent Application (PTO-152)
- 6) Other: \_\_\_\_\_.

**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 3/31/05 has been entered. Applicant's amendment and response filed concurrently with the request for RCE have also been entered. New claims 36-52 have been added. Claims 1-52 are pending and currently under examination.

Please note that the examiner of record for this application has changed, see the last page of this office action.

Upon review of the pending claims, the examiner of record finds that claims 1-35, previously identified as allowable, are subject to the following rejections or objections. New claims 36-52 are also subject to rejection/objection. See below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 2, 4, 17-18, 20, 22, 35, 37, 50, and 52 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The applicant claims an expression vector or DNA vector encoding a modified human Factor VII polypeptide comprising an enzymatic cleavage site susceptible to cleavage by SKI-1, wherein said enzymatic cleavage site is located in the area of about amino acid 147-154 of said Factor VII and wherein at least one amino acid mutations have been made in said area to create said enzymatic cleavage site, and methods of promoting blood coagulation by administering said DNA vector to the individual. The applicant further claims said vectors and methods wherein the amino acids 151-154 of human Factor VII have been replaced with the amino acid sequence of SEQ ID NO:9.

The specification is primarily directed to modifying the Factor VII nucleic acid sequence such that it is capable of expressing a modified Factor VII polypeptide which contains a furin cleavage site located in the area of amino acid 147-154 of the wild type Factor VII amino acid sequence. While the specification further discloses that the Factor VII nucleic acid sequence can be modified such that it is capable of expressing a modified Factor VII polypeptide which contains an SKI-1 cleavage site located in the area of amino acid 147-154 of the wild type Factor VII amino acid sequence, and preferably wherein amino acids 151-154 of human Factor VII have been replaced with the amino acid sequence of SEQ ID NO:9, the specification fails to provide an enabling disclosure that replacement of amino acids 151-154 of the wild type human

Factor VII amino acid sequence with the amino acid sequence of SEQ ID NO:9 would in fact result in a modified Factor VII polypeptide capable of being cleaved by SKI-1. In regards to the specific replacement of amino acids 151-154 with SEQ ID NO:9, it is first noted that Figure 3 in fact shows the replacement of amino acids 147-154, not amino acids 151-154 with the amino acids of SEQ ID NO:9. Further, the working examples provide only a brief prophetic description on page 26 of modifying the amino acid sequence of Factor VII around amino acid 152 to include an SKI-1 cleavage site. Other than SEQ ID NO:9, the specification does not provide any guidance as to any other sequence which is capable of being cleaved by SKI-1 in the context of any protein including a modified Factor VII protein. Thus, the specification, while broadly disclosing the additional SKI-1 cleavage sites, only provide description for SEQ ID NO:9, and further fails to demonstrate that any protein including Factor VII which contains the amino acid sequence of SEQ ID NO:9 is capable of being cleaved by SKI-1.

At the time of filing, SKI-1, which stands for subtilisin/kexin isozyme-1, was a novel proprotein convertase. The literature published prior to the effective filing date of this application teaches that SKI-1 has a unique cleavage specificity from other proprotein convertases. Seidah et al. teaches that at the time of filing, the cleavage site for SKI-1 cleavage was determined to be (R/K) -X-X-(L/T)↓ (Seidah et al. (1999) Brain Research, Vol. 848, 45-62). The applicant does not teach this consensus cleavage sequence. Instead the specification teaches the concensus sequence (R/K) -X -(R/K)-(L/V/F) -Z (SEQ ID NO:20), which is found in SEQ ID NO:9 as claimed (see Figure 3). Thus the concensus cleavage sequence for SKI-1 does not correspond to that disclosed in the literature at the time of filing. Therefore, in view of the teachings of Seidah et al. that the SKI-1 cleavage is (R/K) -X-X-(L/T)↓ , the skilled artisan would not have

predicted that a sequence which does not contain this concensus cleavage site would be capable of being cleaved by SKI-1. As such, in view of published concensus cleavage sequence for SKI-1, the breadth of the claims, and the lack of working examples which demonstrate that alternate cleavage concensus sequences for SKI-1 cleavage exist and in particular that SEQ ID NO:9 is capable of being cleaved by SKI-1, it would have required undue experimentation to practice the invention as claimed.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 18-19, 21, 36, and 51 are rejected under 35 U.S.C. 102(e) as being anticipated by WO 01/70763 A1 (2001), hereafter referred to as High et al., which designated the United States and was published in English, and which claims priority to US provisional application 60/191,331, filed 3/22/00.

It is noted that the previous examiner withdrew the rejection of claim 1 under 35 U.S.C. 102(e) over High et al. based on applicant's arguments that High et al. teaches the insertion of the furin cleavage site into the endogenous Factor VII cleavage site rather than the mutation of

the endogenous amino acids at the Factor VII cleavage site to allow cleavage by furin. However, the examiner now of record finds that the claims as written are clearly read on the vectors and methods disclosed by High et al. as discussed in detail below.

The applicant claims an expression vector or DNA vector encoding a modified human Factor VII polypeptide comprising an enzymatic cleavage site susceptible to cleavage by furin, “*...wherein said enzymatic cleavage site is located in the area of about amino acid 147 through about 154 of said Factor VII and wherein at least one amino acid mutations have been made in said area to create said enzymatic cleavage site*” , and methods of promoting blood coagulation by administering said DNA vector to the individual.

High et al. teaches expression vectors, including DNA vectors such as plasmids, adenoviral vectors, and adeno-associated viral vectors, which comprise a nucleic acid encoding a modified human Factor VII in contains a furin cleavage sequence at the endogenous Factor VII cleavage site ( High et al., pages 4, 6, 9, 10, 15, and 41-44). Specific furin cleavage sequences identified by High et al. include RKR, and RKRRKR (High et al., page 15). While the claims recited on page 41-44 of High et al. teach inserting the furin cleavage site between amino acids 152-153 of Factor VII, High et al. also teaches that, “[t]he position of the engineered proteolytic cleavage site within the modified blood clotting factors of the invention will likely be the same as the natural wild type (native) proteolytic cleavage site. That is, the engineered cleavage/recognition site will substitute for the native cleavage/recognition site” (High et al., page 15, lines 13-16). Thus, High et al. teaches both the insertion of a furin cleavage sequence between amino acids 152-153 or the substitution of a furin cleavage sequence for the native cleavage site. Both of these embodiments are encompassed by the applicant’s claims as written.

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In particular, please note that the mutation of one or more amino acids within amino acids 147-154 of Factor VII includes simple substitution of one amino acid residue for another or the insertion of additional amino acids to this area. That the claims read on mutations including the addition of amino acids is clear from claims 5, 26, and 41 which recite that amino acids 147-154 are replaced by the amino acid sequence of SEQ ID NO:5 - SEQ ID NO:5 adds an additional amino acid to the length of the protein.

In addition, High et al. teaches that the expression vectors/DNA vectors contain liver specific promoters (High et al., page 9, and page 43, claim 27). Finally, High et al. teaches the administration of the vectors for the treating of bleeding or clotting disorders in mammals such that the modified Factor VII expressed in the mammal is cleaved to produce Factor VIIa which increases blood clotting (High et al., pages 5, 7, and 9). Thus, by teaching all the elements of the claims as written, High et al. anticipates the instant invention as claimed.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4, 20, 22, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/70763 A1 (2001), hereafter referred to as High et al., which designated the United States and was published in English, and which claims priority to US provisional application 60/191,331, filed 3/22/00, in view of Seidah et al. (1999) Brain Research, Vol. 848, 45-62.

The applicant claims an expression vector or DNA vector encoding a modified human Factor VII polypeptide comprising an enzymatic cleavage site susceptible to cleavage by SKI-1, “...wherein said enzymatic cleavage site is located in the area of about amino acid 147 through about 154 of said Factor VII and wherein at least one amino acid mutations have been made in said area to create said enzymatic cleavage site”, and methods of promoting blood coagulation by administering said DNA vector to the individual.

High et al. teaches expression vectors, including DNA vectors such as plasmids, adenoviral vectors, and adeno-associated viral vectors, which comprise a nucleic acid encoding a modified human Factor VII which contains a non-native proteolytic cleavage site at the endogenous Factor VII cleavage site ( High et al., pages 4, 6, 9, 10, 15, and 41-44). High et al. also teaches that, “[t]he position of the engineered proteolytic cleavage site within the modified blood clotting factors of the invention will likely be the same as the natural wild type (native)

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proteolytic cleavage site. That is, the engineered cleavage/recognition site will substitute for the native cleavage/recognition site" (High et al., page 15, lines 13-16).

In addition, High et al. teaches that the expression vectors/DNA vectors contain liver specific promoters (High et al., page 9, and page 43, claim 27). Finally, High et al. teaches the administration of the vectors for the treating of bleeding or clotting disorders in mammals such that the modified Factor VII expressed in the mammal is cleaved to produce Factor VIIa which increases blood clotting (High et al., pages 5, 7, and 9).

High et al. differs from the instant invention by failing to teach the addition of an SKI-1 cleavage site. While High et al. provides specific examples for modifying the Factor VII polypeptide to include a furin cleavage site, High et al. clearly provides motivation for using amino acid sequences recognized by any intracellular protease located in the endoplasmic reticulum-golgi transport pathway which is known in the art (High et al., page 14, lines 31-32).

Seidah et al. supplements High et al. by teaching that aside from furin, many proprotein proteases were known in the art, including SKI-1 (Seidah et al., abstract, and 49-50). In particular, Seidah et al. teaches the consensus amino acid recognition site for SKI-1 cleavage (Seidah et al., abstract, and page 58). Therefore, in view of the motivation provided by High et al. that human Factor VII can be modified at its endogenous cleavage site to include an amino acid sequence recognized by any intracellular protease located in the endoplasmic reticulum-golgi transport pathway which is known in the art, it would have been *prima facie* obvious to the skilled artisan to substitute the SKI-1 amino acid cleavage site for the furin site in the vectors and methods taught by High et al. Further, in view of the teachings of Seidah et al. that polypeptides containing the SKI-1 amino acid cleavage site are in fact cleaved by SKI-1, the skilled artisan

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would have had a reasonable expectation of success that inserting or substituting the SKI-1 amino acid cleavage site for the endogenous Factor VII cleavage site would result in a polypeptide capable of being cleaved by SKI-1.

***Allowable Subject Matter***

Claims 5-16, 23-34, and 38-49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

***Information Disclosure Statement***

The information disclosure statement filed 3/31/05 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It is noted that citation no. 21 (EP 0 775 750) is in German and further that no translation has been provided. Citation 21 has therefore not been considered by the examiner and is crossed out on the attached IDS.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D  
PRIMARY EXAMINER

